

## Historical Review

### EARLY HISTORY OF IRON DEFICIENCY

Iron deficiency has been described as 'probably the most frequent nutritional deficiency in the world' with perhaps 2 billion individuals across the world suffering the most obvious outcome – iron deficiency anaemia (IDA) (Hallberg *et al*, 2000). In its more severe forms, IDA leads to significant symptomatology and is accompanied by profound pallor. Yet anaemia as a specific cause of pallor seems rarely to have been discussed in early medical writing, perhaps because both anaemia and pallor were common to the late stages of many serious conditions. Today, signs suggestive of anaemia can be confirmed by the quick, more or less routine measurement of haemoglobin concentration. Without such testing, confirmation of anaemia is impossible and, without sophisticated biochemistry or stained bone marrow aspirate, confirmation of iron deficiency is likewise impossible. As a consequence, hypochromic microcytic anaemia was only fully recognized as iron deficiency potentially of dietary origin in the 1930s. Clinical consequences of iron deficiency without anaemia are still in the process of being defined. Our discussion will therefore focus on early developments leading to the recognition of IDA and the realization that disease can result from dietary deficiency of the fourth most common element in the world.

### PREHISTORY

Was early man affected by IDA? Prehistoric human skeletal remains frequently show many small holes in the compact outer bony layers of the skull together with widening of the diploë. This condition, known as porotic hyperostosis (PH), resembles the bony findings in inherited anaemias but is widespread in regions such as northern Europe and North America where genetically determined anaemias are uncommon. Stuart-MacAdam (1992) therefore argued that PH indicates IDA in these remains. This view is supported by PH increasing in prevalence with archaeological evidence for communities moving from hunter-gatherer to agricultural societies, particularly when they took up the culture of maize – a very poor source of absorbable iron. It is suggested that the iron deficiency causing PH occurs predominantly in infancy. The moderate increase in erythroid precursors (Pippard, 1996), stimulated by iron deficiency and anaemia, and occurring in bone marrow already fully involved in erythropoiesis, leads to thinning of the outer table of the skull and erosion in areas such as the roof of the orbit (cribria orbitalis) and the parietal bones (Stuart-MacAdam, 1991; Aufderheide & Rodriguez-Martin, 1998). PH in later life may be the failure of these early bone changes to resolve. The effects of infection and infestation would exacerbate the effects of the dietary deficiency so PH

might then indicate a population's total pathogen load rather better than its dietary iron intake. Such an interpretation could explain the high rates of PH in skeletons from deprived areas of eighteenth- and nineteenth-century London (Stuart-MacAdam, 1992). Studies from Nubia seem to link iron deficiency with *cribria orbitalis* (Sandford *et al*, 1983).

### RECOGNIZING ANAEMIA IN IDA

Most symptoms and signs of anaemia are non-specific: tiredness, lethargy, loss of appetite, depression, pallor, breathlessness on exertion. One specific feature of iron deficiency, koilonychia, comes from a twentieth-century description by Kaznelson (Davies, 1931) although it is represented in the ancient 'Lydney hand'. This bronze model of a forearm, presumably a votive offering, was unearthed at a Celtic shrine next to a Roman iron mine in Lydney Park, Gloucestershire, and shows spoon-shaped nails, suggesting a connection between the supplicant and iron deficiency (Hart, 1981, 2001).

Iron-containing chalybeate (named after the Chalybes, skilled iron workers in Roman Asia Minor) waters have been recognized for their healing properties since prehistoric times. Many British spa towns owe their fame to chalybeate springs. Some, such as Bath (Aqua Sulis) and Llandrindod Wells (Balnes Siluria – the baths of the Silurians) are pre-Roman. We tend to overlook the iron content of water when evaluating diets today, but the iron salts in these chalybeate waters may have contributed significantly to their healing qualities as they were considered especially beneficial for conditions that we now associate with anaemia. By chance, rather than by design, the treatment recommended was appropriate long before IDA was understood.

Despite the importance of chalybeate waters for healing, the role of iron in haemoglobin formation and red cell function took centuries to be recognized. Swammerdam's (1637–80) sighting of very minute globules in the blood of a frog in 1658 and Malpighi's (1628–94) similar findings 4 years later (Di Guglielmo, 1958; Bessis & Delpech, 1981) were followed by Anthony van Leeuwenhoek's (1632–1723) detailed descriptions of cells in blood. What were these globules or cells for? William Harvey (1578–1637) had postulated the circulation of the blood in 1628 but had to speculate on the presence of capillary connections between the arteries and veins. Malpighi, again in a frog, demonstrated the capillary circulation through the lungs (Bessis & Delpech, 1981). Richard Lower's (1631–91) hypothesis that red cells transported the non-nitrogenous component of air was largely disregarded (Wintrobe, 1980).

Thus, although Antoine Lavoisier (1743–94) showed that blood changed from a dark purply hue ('blue') to bright red with oxygenation, it was almost 200 years after Lower that the German biochemist Felix Hoppe-Seyler (1825–1895) showed, by absorption spectrometry, that haemoglobin is a complex of haematin and protein. Stokes (1819–1903), a Lucasian Professor of Mathematics (!) at the University of Cambridge, developed this work further to show two forms of haemoglobin and the changes between them in response to oxygen administration (London, 1980). Finally, the pioneering work of Paul Ehrlich (1854–1915) developing aniline dyes to stain blood films at last made possible the study of blood cell morphology and the birth of modern haematology (Wintrobe, 1985).

Techniques for counting red blood cells (RBCs) existed long before blood films could be stained and studied in detail. In contrast, the accurate measurement of haemoglobin levels was a twentieth-century development (Wintrobe, 1980). This may explain why it took so long to recognize the anaemia of IDA, let alone the iron deficiency. Red cell counts remain close to normal in IDA, even when cell size and mean cell haemoglobin concentration (MCHC) are dramatically reduced. Pernicious anaemia (PA) was the clinical model for a specific anaemia with low RBC and white blood cell (WBC) counts and gastric atrophy. The discovery of gastric hypochlohydria in some middle-aged women with hypochromic anaemia created an analogy with PA and consequently diverted late nineteenth-century attention from the hypochromic anaemia to gastric physiology.

#### UNDERSTANDING OF THE ROLE OF IRON IN IDA

Before the twentieth century, most developments in the biochemistry of iron seemed to parallel, rather than complement, haematological developments. In 1713, Lemyer and Geoffroy and, in 1747, Menghini burnt blood to ash and found residual particles that were attracted by lodestone and thus presumed to be iron (London, 1980; Widdicombe, 2001). Substances that were universally available in the environment, such as iron, were assumed to be ingested in adequate quantities. When Lusk (1917) commented that American families consumed between 7 and 35 mg of iron daily, he appeared to imply that, if this was what was consumed, it was evidently sufficient. Failure to recognize dietary iron deficiency might have been compounded by the dominance of Justus von Liebig (1803–73, Fig 1), Professor of Organic Chemistry at the University of Giessen, whose extensive and detailed studies of animal physico-chemical systems heralded the science of biochemistry. Liebig's view, that minerals in the body came preformed as organic compounds derived from plant foods, was widely accepted (Liebig, 1842) and propagated. As late as 1906, Curtis wrote 'the plant can make organic matter out of inorganic elements, just this the animal cannot do at all' (Curtis, 1906). To Russell Henry Chittenden (1856–1943), a founder of the American Physiological Society, inorganic salts in the diet, apart from minerals deposited in bones and teeth, were merely 'aids to nutrition' (Chittenden, 1907).

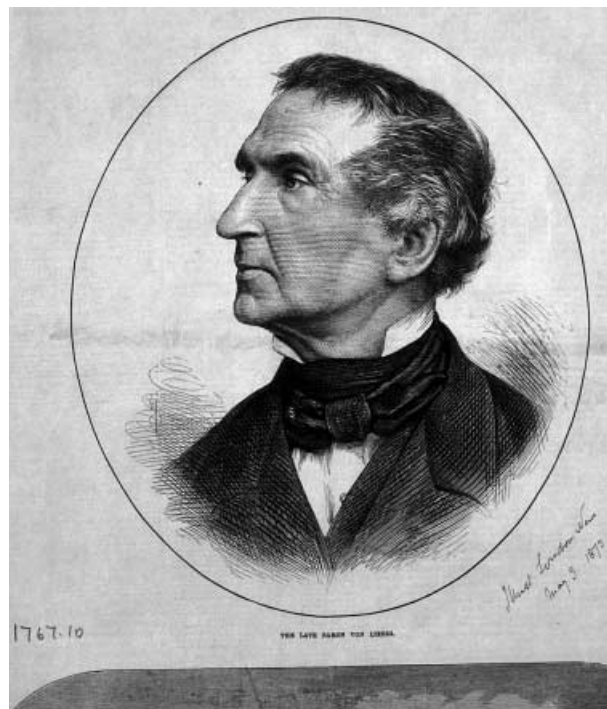


Fig 1. Justus von Liebig. Wood engraving 1873. ©The Wellcome Library, London.

Gustav von Bunge (1844–1920), Professor of Physiological Chemistry at the University of Basle, who became the voice of organic chemistry after Liebig, expressed uncertainty over Liebig's views on the irrelevance of inorganic iron to nutrition (Bunge, 1902). His somewhat confused writing on iron nutrition suggests that he had difficulty developing his views on the role of iron in the prevention of anaemia, providing little support for his reputation as the first to suggest that hypochromic anaemia was caused by iron deficiency. In his *Pathological and Physiological Chemistry*, Bunge admits 'that the habitual consumption of foods poor in iron may lead to anaemia, is possible' but he goes on to contradict this by stating 'it is difficult to imagine a diet that would not contain the small amounts of the metal required daily'. In extensive studies, Bunge showed that human milk was very low in iron. Newborn infants had much higher concentrations of iron in the liver and kidneys than older infants, children or adults. He recognized high concentrations of iron in spinach, egg yolk, beef, apples and lentils. He questioned whether the iron in bran was well absorbed because, if so, wholemeal bread would be preferable to white bread. Slightly surprisingly, he also stated that iron from haemoglobin in meat was poorly absorbed, very much in contrast to today's evidence for the specific rapid absorption of haem, and the iron that it carries, from the gastrointestinal tract (Bunge, 1902).

Despite stating that dietary iron deficiency was almost unimaginable, Bunge considered that no food was rich enough in iron to be an effective treatment for deficiency (Bunge, 1902). In what seems like an early appeal for

evidence-based medicine. Bunge questioned the vaunted success of iron salts in the treatment of hypochromic anaemia and chlorosis. 'It is not sufficient to say experience has been made. We must know how it is done. *Where are the control experiments? Where are the statistics?*' (Bunge, 1902: present author's italics).

Aberhelden, a pupil of Bunge, did eventually show that inorganic iron could be absorbed from the gastrointestinal tract, but views were slow to change. Thus, Hutchison (1923) reflected the views of many when he stated that 'iron contained in haemoglobin and its derivatives is very ill absorbed', and he cautioned those adopting the haemoglobin preparations that were being used in the early twentieth century to treat anaemia. Hutchison (1923) quoted experiments in which dogs that were fed with meat had more iron in their bodies than those that were fed with milk. Reflecting Bunge's views, he concluded illogically that the environment itself provided sufficient iron for supplementation (of men or dogs) to be unnecessary. Yet, at the same time, Helen Mackay (1891–1965) was gathering data in post World War I Vienna for her concept-changing work on anaemia in infancy (see later).

#### DIETARY IRON INTAKES IN THE PAST

Our assumption has been that, in historic times, the iron content of the diet was no better, and possibly worse, than today. This may not have been so. In the 1860s, the American Civil War led to massive depression in the Lancashire cotton industry and extensive poverty and famine (Fig 2). In 1863, Edward Smith (1818–74; Fig 3) was sent to enquire into the diets of cotton operatives in order to determine the least amount of food needed to ward off starvation among the unemployed. Smith later extended his remit to cover dietary data from 741 workers' families in Yeovil, Macclesfield and London (Barker *et al.* 1970).

Barker *et al.* (1970) have reviewed Smith's data and compared nutrient intakes with those recorded for working

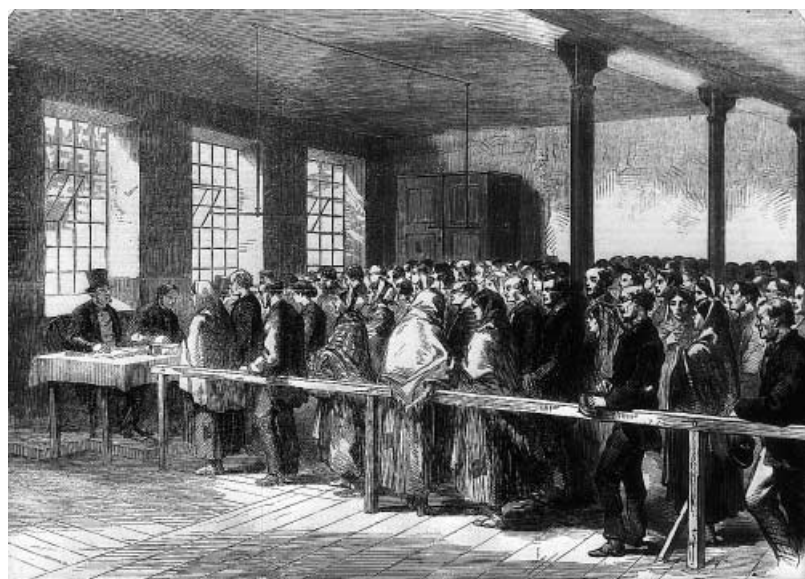
class families with four or more children from the 1965 Household Food Consumption and Expenditure Survey (Department of Health & Social Security, 1967) and from a 1930s survey looking at nutrient intakes among the urban disadvantaged (Boyd Orr, 1936). Estimated iron intakes were higher in the 1860s than in the 1930s or 1960s (Barker *et al.* 1970). Estimated intakes in the 1860s were 12.5 mg/d for indoor workers and 15.9 mg/d for rural workers: 50% more iron than in the diets of the urban poor in the 1930s (Boyd Orr, 1936). Barker *et al.* (1970) concluded that the prevalence of severe IDA in the nineteenth century must have resulted from defects in absorption or metabolism rather than deficient iron intake, reflecting perhaps the high phytate content of diets and the high prevalence of infection in the nineteenth century.

#### THE CLINICAL PICTURE

Several conditions involving iron deficiency have waxed and waned in prevalence and clinical interest over the last 150 years. Chlorosis, for example, preoccupied many clinicians between the seventeenth and early twentieth centuries and yet is not seen today. Achlorhydria with hypochromic anaemia in middle-aged women and hypochromic anaemia complicated by post-cricoid web (Plummer–Vinson or Brown Kelly–Patterson syndrome) are two other entities that seem to be less common today than in the past. Does iron deficiency present with different symptomatology today and, if so, why? Or did the prolonged and severe iron deficiency of earlier times lead to clinical features which, in today's scientifically more specific era, rarely have time to develop?

#### *Chlorosis*

Chlorosis (also the 'green sickness', *morbus virgineus*, *mal d'amour* and other names) was described in relatively modern times as 'a hypochromic anaemia in adolescent girls usually associated with gastrointestinal and menstrual



**Fig 2.** The cotton famine: distributing tickets for bread, etc. at the office of the District Provident Society, Manchester. From *Illustrated London News* 1862, 41, 52. ©The Wellcome Library London.

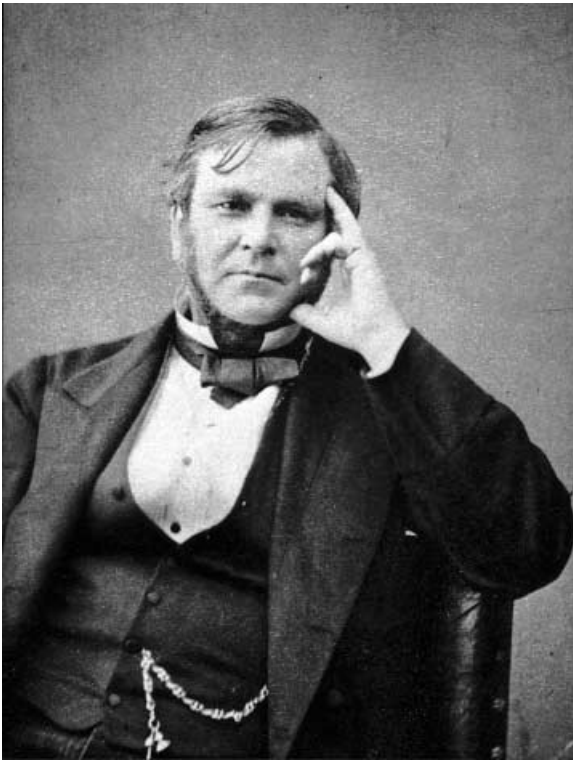


Fig 3. Edward Smith. From Barraud & Jerrard, *The Medical Profession in All Countries*, Vol. 2, 1874. ©The Wellcome Library London.

disorder' (Patek & Heath, 1936) The first description is often dated to Johann Lange in 1554, but the condition was described frequently between the middle of the seventeenth century (Hart, 2001) and the end of the nineteenth century. Then, around the turn of the nineteenth century, chlorosis disappeared.

The green appearance described by some clinicians has made it difficult to explain chlorosis away as simply IDA. Today, we do not regard even severely anaemic individuals as green. The Shorter Oxford English Dictionary (1993) includes a definition of 'chlorosis' from the early nineteenth century as blanching of the normally green parts of plants or greening of parts that are normally pale. Have we been misled? Was the green colouring less of a feature, and extreme pallor more of a feature, in chlorosis than has sometimes been stated? We are perhaps supported in this view by Hirsch's comment, where he quotes Sennart (writing in 1760) stating that 'pallor or yellow tinge to the skin' was a sign of chlorosis (Hirsch, 1885) and, in 1915, Cabot, cited by London (1980), also questioned the olive green colour and described affected brunettes presenting with a yellowish pallor and affected blondes with a whitish pallor. However, others cite the term Chlorus applied to Constantius the father of the Emperor Constantine (Hart, 2001) – but was he 'olive skinned' or pale? Or does the nickname perhaps have other connotations as Cicero refers to a Sextus Pompeius, also known as Chlorus (Cicero, 2002). The description may have related to geographical activity as a soldier, as Chlorus was a river



Fig 4. John Coakley Lettsom, 1787. Engraving by Thomas Holloway. ©The Wellcome Library, London.

in Cilicia. Hart (2001) cites the eminent US physician W. Crosby's 1955 case of anaemia with green discoloration, which he explained as combined protein and iron deficiency. From such a provenance, green coloration must be accepted. Yet, in conditions such as gluten-sensitive malabsorption, where there may be protein deficiency as well as iron deficiency, green coloration is not described.

Most features of chlorosis fit well with severe IDA in adolescent girls and young women. Long before the microscopy of stained blood was commonplace, Gabriel Andril (1797–1876) had commented on the very small red cells in chlorosis (Wintrobe, 1980). John Coakley Lettsom (1744–1815; Fig 4), a successful physician who founded the London Society of Medicine and the Royal Seabathing Hospital at Margate among other institutions, wrote reassuring tracts on a number of common medical problems, including one on chlorosis in girls' boarding schools. As one of seven pairs of twins born to a West Indian planter's family, Lettsom attended a Quaker boarding school in England from the age of six, so perhaps had insight into the environment his cases were experiencing (Hunt, 1972). He described the features of chlorosis as paleness and sallowness of complexion, palpitations of the heart, difficulty breathing on exertion, bloated appearance, loss of appetite, reluctance to exercise and amenorrhoea (Lettsom, 1795). Amenorrhoea is difficult to explain except that delayed puberty can be a feature of severe anaemia, and amenorrhoea features in severe malnutrition.

One hundred years later, Stockman (1895) expressed the view that absence of light, fresh air and exercise together with unhealthy excitement were predisposing, rather than direct, causes of chlorosis. Haemoglobin levels (still very inaccurate) were always low, and RBC counts were often reduced with ill-formed, small cells. Fifty per cent of his 63 cases had some dyspepsia. Mean dietary iron intakes for 15 non-chlorotic girls were 6–8 mg/d, whereas for two chlorotic girls, mean intakes were 2.6 and 1.2 mg/d respectively. Stockman concluded that excessive menstrual loss together with habitually low intakes of iron from the diet were the direct causes of chlorosis. Treatment was iron (Stockman, 1895).

Despite Stockman's views, chlorosis continued to be perceived as associated with developing sexuality in teenage girls. Weber & Parkes Weber (1907, pp. 641–647) talk of a temporary disorder of haematopoietic function connected with the development of the reproductive organs. Others had more bizarre explanations. Lettsom (1795) had attributed chlorosis to tight stays (among other issues), and Wintrobe (1980) commented that the disappearance of chlorosis at the end of the nineteenth century was attributed more to the disappearance of tight corsets than to any economic or environmental change.

Iron deficiency may not have been recognized as causal but the use of iron in the treatment of chlorosis had been common practice for centuries (Hart, 2001). Sydenham (1624–89) advocated the use of 'chalybeate' – iron filings steeped in cold Rhenish wine, strained, sweetened and boiled to the consistency of syrup (London, 1980). The virtue of chalybeate waters for the treatment of chlorosis was widely publicized. Thus, at Spa in Belgium (which gave the British a generic name for health resorts), the chief 'affections' treated were chlorosis and anaemia (Weber & Parkes Weber, 1907, pp. 496–503). The waters were reported to contain between 0.07 and 0.27 per mille (parts/thousand) bicarbonate of iron. The spa social life could take over the healing activities, so bad cases of chlorosis were sometimes advised to take pharmaceutical preparations to assist the effect of the climate, 'especially if the mineral waters seem not to agree' (Weber & Parkes Weber, 1907, pp. 496–503).

In 1832, Blaud introduced pills containing 1.39 g of ferrous sulphate and 0.1 g of potassium carbonate, and these became widely recommended for chlorosis and other conditions (Blaud, 1832). The original pills contained 64 mg of iron but later often included arsenic (added deliberately). Many physicians, even into the 1930s (Thomson & Findlay, 1933), and including (much earlier) Osler, thought iron was more effective if combined with arsenic. Nevertheless, as already mentioned, organic chemists such as Bunge expressed considerable doubt about these and other iron remedies in chlorosis and hypochromic anaemia, probably delaying the real understanding of IDA (Bunge, 1902).

Why did chlorosis 'die out'? The disappearance of stays and tight corsets seems an unlikely explanation. Was it a result of improved diet, better social circumstances and reduced infection? Did effective treatment with iron prevent

very severe iron deficiency becoming chronic? We cannot be sure. Occasional patients are still seen today with dietary iron deficiency and haemoglobin levels below 4.0 g/dl. But they are not green. Did the green colour act as a 'red herring'?

#### *Simple achlorhydric anaemia*

At the end of the nineteenth century, interest turned from counting red cells in anaemia to investigating the gastrointestinal physiological changes. The finding that some middle-aged women presented with poor appetite, achlorhydria and hypochromic, microcytic anaemia created a prolonged debate over whether the anaemia was a specific disease condition. Taylor & Wells (1905) seemed close to the current concept of IDA when discussing (rather briefly) 'simple primary anemia' (spelt thus despite English publication), the existence of which had been doubted by some, although 'many describe it as a special condition'. They commented on the lack of specific pathology, but similar symptomatology to chlorosis and other conditions where there was 'diminution of the blood or of its normal elements'. To these authors, simple primary anemia was the consequence of poor hygiene. Rapid recovery took place when the patient received 'fresh air, proper food and exercise' (Taylor & Wells, 1905).

The association of achlorhydria and iron deficiency is still not well explained. Normal mitochondrial function is dependent on adequate iron. In deficiency, haem-containing cytochromes in epithelial cells become iron depleted. Epithelial abnormalities then develop in buccal, oesophageal and gastric mucosae, although the severity of changes correlates poorly with tissue enzyme levels (Jacobs, 1961). Oesophageal epithelial 'webs' disappear only slowly, if at all, on iron repletion. Thus, iron deficiency could be a primary cause of gastric atrophy and achlorhydria, but gastric atrophy and achlorhydria could also lead to reduced iron absorption and iron deficiency. The early twentieth-century focus on achlorhydria in the hypochromic anaemia of middle-aged women is difficult to unravel.

Understanding of IDA by the early 1930s can be summarized by the Americans, Wintrobe & Beebe (1933). They stated that 'there is only presumptive evidence that idiopathic hypochromic anemia develops because an individual is unable to meet the demands for haemoglobin or replace the normal loss of blood on account of defective utilization of blood building materials in the diet'. Once again, the concern: was hypochromic anaemia a specific disease process? Yet this was the era when micronutrient deficiencies had been recognized. Further, haemorrhagic conditions were known to lead to hypochromic microcytic anaemia, so the relevance of balancing iron intakes with needs might have been made.

It was in 1931, with papers by Davies (1931) and Witts (1931), that the role of iron in hypochromic anaemia in adults was properly defined. Davies (1931) even extended the role of iron as, if changes in the cutaneous and epithelial structures (nails, tongue, oesophagus) of women with achlorhydria and anaemia improved with iron therapy, 'further functions must be

attributed to iron in the maintenance of general nutrition'. He drew attention to the poor diet that commonly occurred in women with achlorhydria and the common (but not universal) finding of achlorhydria in association with an anaemia that was responsive to large doses of iron. He concluded correctly that 'the important aetiological features then are the deficient diet poor in iron, the achlorhydria with its impaired absorption of iron and the simple anaemia with its deficient haemoglobin and its therapeutic response to iron. All these support the conception of a primary iron deficiency as the essential cause' (Davies, 1931).

Witts (1931) struggled more with the concept of chronic microcytic anaemia as a primary dietary deficiency disease but did explain the anaemia as the inability to form haemoglobin in association with reduced free iron in the blood. He commented that 'it is not possible to ascribe the anaemia solely to defective diet', but many of the women were 'ingesting insufficient iron from their food' (Witts, 1931). He also suggested three ways by which achlorhydria might contribute to hypochromic anaemia. Achlorhydria could cause loss of appetite. The absence of free acid in the stomach could impair iron absorption. Finally, an 'asthenic diathesis' was frequently associated with the anaemia. Gluten-sensitive enteropathy was not recognized as such in 1931, but perhaps this could account for the 'asthenic diathesis' with microcytic anaemia.

#### 'Plummer-Vinson/Brown Kelly-Patterson syndrome'

Both Witts (1931) and Davies (1931) recognized the association of microcytic anaemia with dysphagia and post-cricoid web. Although the syndrome was almost certainly first described in the modern literature by Brown Kelly & Patterson in 1919, a recent lively correspondence has suggested that the rivals for the eponymous name of the syndrome (Plummer and Vinson) actually described a case of dysphagia and anaemia which they attributed to hysteria (Baron, 1991; Slater, 1991; Logan, 1992). This nomenclature argument may be entirely spurious as Logan (1992) claims that post-cricoid web dysphagia was first described by Baillie in 1793!

Whoever described it first, post-cricoid web was a widely recognized combination of glossitis, oesophageal dysphagia and iron deficiency anaemia. Yet today it is an unusual finding. Was it a real disease entity? Elwood *et al* (1964) screened a Welsh village for dysphagia and post-cricoid web and recorded higher haemoglobin levels and MCHC in those with post-cricoid web than in those without the finding. Nevertheless, current views are that iron deficiency caused the buccal, oesophageal and gastric mucosal epithelial abnormalities. Oesophageal abnormalities have been associated with circulating parietal cell antibodies, achlorhydria and an increased risk of pernicious anaemia and may respond only poorly to iron therapy (Pippard, 1996). If chronic iron deficiency was a precipitating cause of Brown Kelly-Patterson syndrome (Chen & Chen, 1994), then the screening for, and vigorous treatment of, IDA in those 'at risk' plus better iron absorption from modern diets might explain the reduced prevalence.

#### DEFINING THE ROLE OF IRON DEFICIENCY

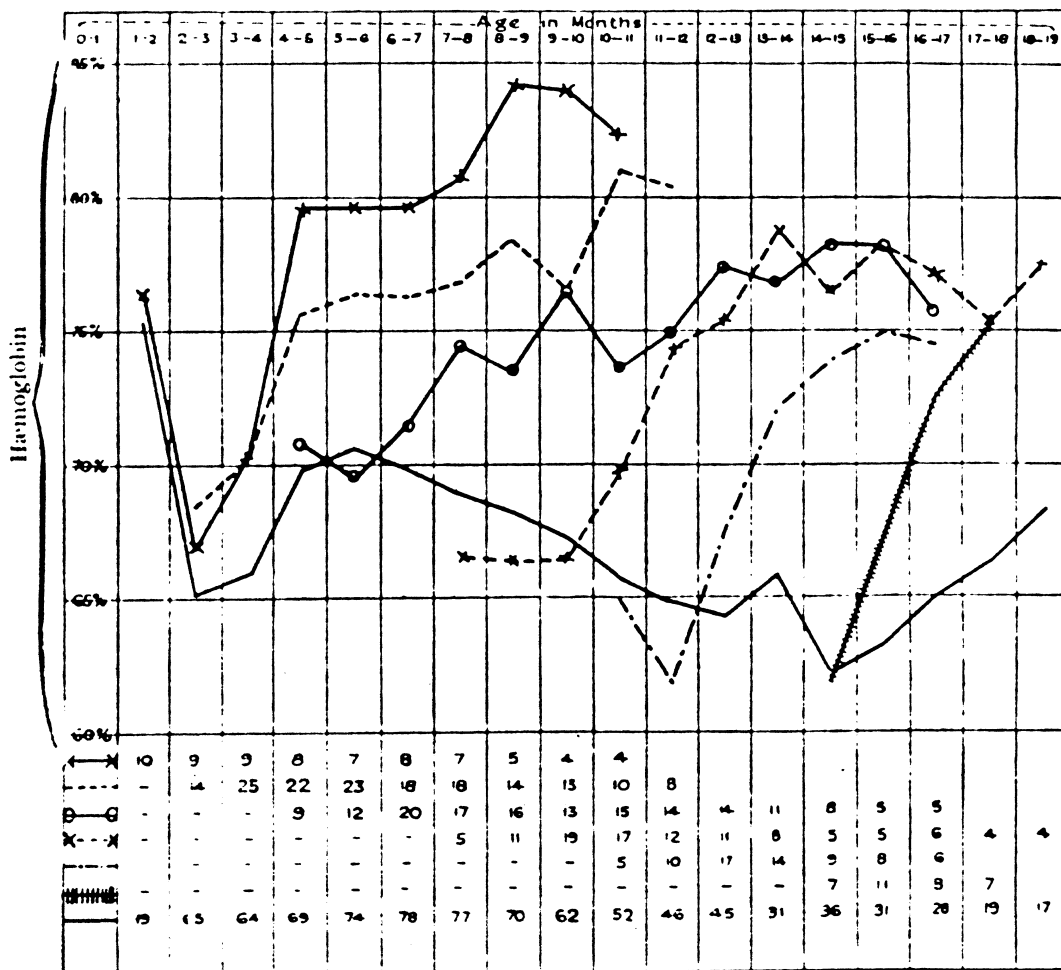
The entities of chlorosis, microcytic anaemia with achlorhydria and anaemia with post-cricoid web are fascinating adjuncts to the development of ideas about iron deficiency and iron deficiency anaemia. However, their clinical peculiarities seem to have obscured the underlying nutritional problem. Confirmation of the importance of iron in the diet for the prevention of hypochromic microcytic anaemia came with developments in paediatrics.

#### *Helen Mackay and the children of East London*

After working in Vienna post-World War I, Helen Mackay, the first woman to receive the fellowship of the Royal College of Physicians of London, studied young children in East London in the 1920s to determine 'normal' haemoglobin values for different stages of infancy (Mackay, 1928, 1931). Mackay (1931) showed high haemoglobin levels at birth, a gradual fall from birth to around 2 months and then (in Mackay's infants), a steady level until further falls from 6 months into the second year. Although the low haemoglobin of late infancy seemed more common and more severe in non-breast-fed than in breast-fed infants, both methods of feeding led to falling haemoglobin levels, hypochromia and microcytosis from 6 months onwards with the most marked falls in low-birthweight infants. As it was not known whether these findings reflected normal physiology or not, trials of likely therapeutic interventions seemed the logical way to resolve the question.

In earlier studies, Mackay (1928) had found that infants attending her clinics gained weight when treated for infection and given supplementary milk. These interventions had not prevented the decline in haemoglobin levels. Supplementation with iron salts, however, produced dramatic changes. The late anaemia of infancy (that is after the physiological post-natal fall) was either prevented or, when iron was started after 6 months, diminished in iron-supplemented infants compared with those not receiving supplementary iron (Fig 5). Mackay (1928, 1931) also remarked that iron-treated infants looked much healthier. Iron-supplemented infants had only around 50% of the episodes of respiratory tract infection, diarrhoea and specific fevers experienced by the unsupplemented infants.

The work of Mackay (1931) is open to criticism when compared with today's gold standard randomized placebo-controlled studies. Her London infants were breast fed, cow milk or formula fed with no supplement, given light therapy or supplemented with iron over variable periods between 1925 and 1927. They were neither studied at entirely the same time nor randomly chosen. Nevertheless, Mackay's studies established the pattern of haemoglobin change in early infancy and demonstrated the nutritional vulnerability of premature infants. She drew very definite conclusions that the anaemia of late infancy resulted from insufficient iron in the diet and could be eliminated by iron therapy. Her recommendation, that iron should be given to non-breast-fed infants from the first months of life because this can support higher levels of haemoglobin later in infancy, stands good today. European Union directives require that all



**NOTE.**—Cases starting treatment from 4 months old onward show in 3 curves a drop preceding the rise. This is due to the fact that new untreated cases are included among these observations. Some infants included in these curves are known to have had no iron medication for a month at a time.

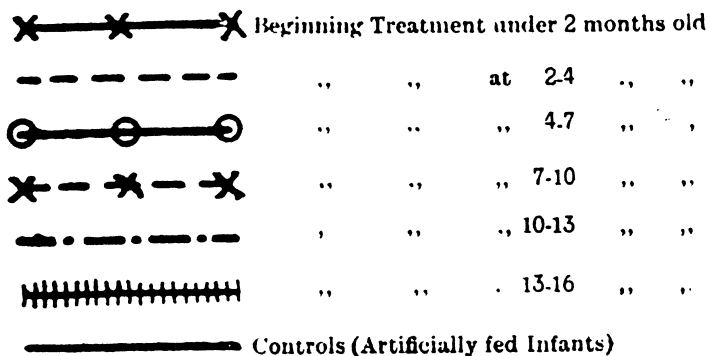


Fig 5. Effect of iron treatment on haemoglobin levels [results presented as a percentage (100% haemoglobin: 14.8 g/dl)] according to age of start of treatment (some values fell initially because of the age spread of the groups and the inclusion of children who had not had time to respond to treatment) in children (not all children in each group had haemoglobin levels measured at every point) studied 1926-7. From Mackay (1928) (with permission).

infant feeding formulas are supplemented with iron and vitamins.

Discussing the work of Mackay, an editorial (Anonymous, 1931) commented on the work of Kotikoff, from Leningrad, who had also published data on iron and haemoglobin levels in infants. He had found a fall in

circulating iron that paralleled that of the haemoglobin level after the first 6 weeks, which continued over the first year of life and was unaffected by either ultraviolet light or cod liver oil! His confusion is typical of the poor nutritional understanding of anaemia that existed before Mackay's publications.

## CONCLUSION

Mackay's studies finally brought iron deficiency and IDA together. The need for adequate iron in the diet was established, and the complicated changes in haemoglobin levels in normal young children were more or less delineated. It became possible to consider not only dietary iron intake, but the effects of gastrointestinal function, other nutrients and other pathology on iron absorption and metabolism. In supplementing infant formulas and breakfast cereals, we acknowledge today the widespread vulnerability of whole populations, even in affluent countries, to potential inadequacies in their diets. Yet we are still ignorant of just how vulnerable populations are to damage from iron deficiency. Iron is intimately involved in many metabolic processes. The specific consequences of iron deficiency, with or without associated anaemia, on immune processes and growth and cognitive function are still poorly defined (Oppenheimer, 2001). We also recognize that excessive dietary iron and inappropriate iron supplementation have adverse effects by initiating unwanted free radical activity. Worldwide, however, the principal clinical concern with iron nutrition remains the same as it did before the role of iron was delineated, namely the identification, treatment and prevention of anaemia in vulnerable groups.

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